Letters

Colonic angiodysplasia

I was very interested by the suggestion by Roskell *et al* that colonic angiodysplasia may be related in some way to abnormalities in vascular basement membrane.[1]

The idea is appealing, and the illustration of staining for type IV collagen does indeed appear to show a difference between the strong positivity in submucosal vessels (fig 1A) and absence in the lamina propria vessels (1B). However, in colonic mucosa there is a basement membrane between the columnar epithelium and the stroma. This contains type IV collagen. If we are to trust the apparent absence of staining of the vascular basement membranes in the lamina propria, can the authors explain why the adjacent epithelial basement membranes also appear to be completely negative in their illustrations?

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1 Roskell DE, Biddolph SC, Warren BF. Apparent deficiency of mucosal vascular collagen type IV associated with angiodysplasia of the colon. *J Clin Pathol* 1998;**51**:18–20.

Authors' response

Dr Furness is correct in pointing out that the epithelial basement membrane in the colon would be expected to stain for type IV collagen, and indeed in all of our cases and controls some staining was seen. However, at the antibody concentration used in our study the epithelial basement membrane staining was very weak and focal compared to the strong staining of the submucosal blood vessels. Indeed epithelial basement membrane staining compared in intensity to the weak staining of the mucosal vessels seen in angiodysplasia.

Our observation of apparent deficiency of type IV collagen in the mucosal vessels is presented as a relative deficiency compared to the strong submucosal vascular staining, and is not compared to the epithelial basement membrane. If we had used a concentration of antibody high enough to result in strong epithelial basement membrane staining sufficient for photography, the differences in vascular staining would not have been visible.

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Immunofluorescent patterns associated with ANCA

We would like to comment on a number of issues raised by Savige *et al* in their recent paper in the Journal.[1]

First, they state that dual positivity for anti-MPO (myeloperoxidase) and anti-PR3 "usually indicates non-specific binding"—that is, a false positive. Our experience is different. We find dual positivity is a relatively rare phenomenon and tends to represent true positivity. This may in part result from our practice to include a control (uncoated well) to check for non-specific ELISA binding. Reviewing our last 500 referred samples reveals only one dual positive. This sample was from a 50 year old female with long standing biopsy proven Wegener's granulomatosis. Immunofluorescence was C-ANCA pattern.

Next, we agree that antibodies such as antimitochondrial and anti-smooth muscle can stain neutrophils, but with the exception of antinuclear antibody (ANA), these rarely mimic true ANCA and seldom cause recognition problems in routine analysis. With regard to the problem of ANA interference, we still find the use of formalin fixed neutrophils helpful in the differentiation of ANA and P-ANCA, though the method has its critics.[2] In our hands, anti-MPO antibodies are rarely formalin negative. A recent review of our data shows that, in a three month period, 0/56 sera showing nuclear stain on ethanol fixed neutrophils and negative on formalin fixed neutrophils (that is, ANA or atypical P-ANCA) were anti-MPO positive. Thus in the context of necrotising vasculitides it offers a quick and useful method for selecting sera for anti-MPO ELISA.

Lastly, Savige *et al* mention a range of atypical immunofluorescence staining patterns, such as the so called "flat cANCA." We are strongly of the view that, while these are of research interest, they should be communicated clearly to ward doctors not as ANCA positive but instead as atypical reactivity of doubtful clinical significance.

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1 Savige JA, Paspaliaris B, Silvestrini R, *et al.* A review of immunofluorescent patterns associated with antineutrophil cytoplasmic antibodies (ANCA) and their differentiation from other antibodies. *J Clin Pathol* 1998;**51**:568–75.
2 Spickett GP, Broomhead V. Formalin fixation and patterns of antineutrophil cytoplasmic antibodies. *J Clin Pathol* 1995;**48**:89–90.

Authors' response

Thank you for the opportunity to reply to Drs Lock and Unsworth. Their letter has highlighted some of the difficulties with ANCA testing that have been addressed by a group of clinicians and scientists in the *International consensus document on ANCA testing and reporting*.[1]

The Consensus document states that the minimum requirements for ANCA testing in new patients are the indirect immunofluorescent (IIF) examination of all sera on normal neutrophils. Sera that contain ANCA, any other cytoplasmic fluorescence, or an ANA that results in a homogeneous or peripheral nuclear pattern should then be tested promptly in ELISA for *both* proteinase 3 (PR3)- and MPO-ANCA.

The Consensus document recommends that reports use the terms "C-ANCA" for cytoplasmic granular fluorescence with interlobular accentuation, "C-ANCA (atypical)" for other types of cytoplasmic fluorescence, "P-ANCA" for any type of perinuclear or granulocyte specific nuclear fluorescence, and "atypical ANCA" for other less common patterns, such as mixed cytoplasmic and perinuclear fluorescence. Antigen specificities are described as PR3- and MPO-ANCA. Reports should indicate that positive neutrophil IIF alone is not diagnostic for Wegener's granulomatosis or microscopic polyangiitis, and that decisions about treatment should not be based solely on the ANCA results.

In reply to specific points raised by Drs Lock and Unsworth:

The ability to distinguish between ANCA and other autoantibodies that stain neutrophils depends very much on the quality of the neutrophil preparation and the skill of the observer. Because of this variability, the consensus document has indicated that all sera that produce positive IIF should be tested in PR3- and MPO-ELISA. The absence of binding in these assays will indicate that the diagnosis of Wegener's granulomatosis and microscopic polyangiitis is unlikely.

With respect to IIF patterns, the consensus document recommends that a "flat ANCA" is called a "C-ANCA atypical." However, it is not always possible to distinguish this from a "C-ANCA" and for this reason ELISA for PR3- and MPO-ANCA should be performed to diagnose Wegener's granulomatosis and microscopic polyangiitis.

The consensus document does not suggest formalin fixation to differentiate between an ANA and P-ANCA. This is because the success of this technique varies in different laboratories, ANA and P-ANCA may occur together, the procedure involves another "run" of IIF, and an ELISA is still necessary if the IIF remains positive, at least to determine the antibody level.

Finally, most laboratories, in Australia at least, use commercial kits for PR3- and MPO-ANCA and do not subtract the binding to uncoated wells for individual sera. Under these conditions "dual positivity" usually represents non-specific binding and is often "borderline" in amount. If background binding is subtracted, then "dual positivity" is more likely to represent a "true" ANCA.

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1 Savige J, Gillis D, Davies D, *et al.* International consensus statement on testing and reporting of antineutrophil cytoplasmic antibodies (ANCA). *Am J Clin Pathol* (in press).

CD-ROM reviews

Topley and Wilson's Microbiology and Microbial Infections, 9th edition (CD-ROM). Edited by L Collier, A Balows, and M Sussman. (£995.00.) Edward Arnold, 1997. ISBN 0 340 70015 7.

Long before the influence of Calman on training, my only guidance for preparation for MRCPath was "read Topley from cover to cover." There were two volumes then. Now there are six. New in the 9th edition are the international authorship, coverage of mycology and parasitology, and the CD version. This is now a massive text to review. I would not expect to find factual fault with any of the contributions from experts, nor did I, even in the areas on which I am qualified to opine. I shall concentrate on the new electronic format.

The CD offers the advantage at least of saving shelf space, but the book becomes "virtual" and there is no feeling of where one is in the text—nor indeed how much of it there is. I find it uncomfortable to read more than a small amount of text from the screen.[1] It was easier to print individual sections that I wanted to study (you can do this for up to 50 paragraphs).

The software allows text searches with varying degrees of complexity, rapid jumps, and personalised electronic annotation and colour highlighting of text. One can cut and paste text (for example references) into personal documents. This does facilitate plagiarism but that is more of a problem in students' assessed work

than in professional skullduggery. However, all the otherwise hidden tags that allow the jumps and popups are carried too.

The quality of the graphics varies from poor to acceptable. Electron micrographs were generally clear and fungal cultures looked good (fuzziness helps). The blood films of malaria did not adequately show dots and clefts. Some of the "extra illustrations exclusive to the electronic version" turned out to be very poor quality line drawings. This was a disappointment. Large tables were particularly tricky to navigate if they did not fit into one screen, and vertical labels were very hard to read. I got round that by highlighting columns in colour blocks—very useful in following a long vertical list of biochemical reactions in the identification of bacteria.

Where the paper reviewer can delight in finding typos, the electronic reviewer has the additional opportunity to look for bugs (even more fun in a book on infection). There are lots. Searching for *Mycobacterium bovis* takes you to all the occurrences of that species but also to *Mycoplasma bovis*. Some jumps don't go anywhere. Eikenella is such a great bacterium that it receives full coverage in two chapters.

Publishers seem to find it convenient to take the word processed text of books and turn them into CDs. They fail to take full advantage of the opportunities presented by electronic publication. We are increasingly used to "point and click." It is a shame the CD version displays lists in almost the same format as the book. The first step has been taken to transform this reference text into electronic format, but as long as the CD version so closely matches the paper version its full potential will never be realised.

These are small gripes. This remains a standard text book that has been improved, expanded and updated. Some imaginative fine tuning would make the CD version clearly the one to buy.

W R GRANSDEN

[1] The CD was run as a single user application on the following equipment, which is about the minimum requirement:
Dell Optiplex PC
Windows 3.11
Ultrascan SVGA monitor 1024 × 768, 256 colours
16 MB RAM
Pentium processor

Atlas of Pathology: Spleen (CD-ROM). By J Diebold, A le Tourneau, J Audouin, T Molina. (£116.04). Springer-Verlag, 1998. ISBN 3540146407

Images are the key ingredient for a histopathological diagnosis—and a picture tells more than a thousand words. Furthermore biology is so diverse that the number of morphological appearances is almost infinite. Therefore it is very helpful to have illustrations next to text on histopathology. An atlas on splenic pathology was badly needed and now there is an atlas on CD-ROM, by Diebold, le Tourneau, Audouin and Molina. These writers have a very long experience in splenic pathology and are therefore able to present an enormous diversity of cases, including very rare disorders. Since such images have not hitherto been available, this is a welcome addition.

The CD-ROM is well organised and one can search the images with an extensive user-friendly search system, based on ICDO codes or SNOMED codes and keywords. The number of search possibilities is probably even larger than needed for this atlas. On the other hand several terms used in the REAL classification on lymphomas are not recognised.

The CD-ROM enables one to find images rapidly (depending on the system one uses) and gives one the opportunity to enlarge an image and add the provided text to it. Since this is basically an atlas, the amount of information with each picture is small. For instance, there is an interesting case diagnosed both as lymphoplasmacytic lymphoma and monocytoid B cell lymphoma. Both morphologies are shown and the following information is given:

M-96713 Malignant lymphoma, lymphoplasmacytic

M-97113 Monocytoid B-cell lymphoma, spleen

Lymphoplasmacytic lymphoma associated with a marginal zone lymphoma. Hematein-eosin. Diffuse infiltration by small lymphoid cells with a dark nucleus. At the periphery, a more pale area constituted by marginal zone cells, some with a monocytoid B cell morphology. Both cells belong to the same clone.

It remains unclear how to classify this case and why. For more information there are several textbooks of course, but some relevant references on each disorder would be very helpful. Only rarely are a few references given.

The quality of the images is overall quite good, although for some (rare) disorders a not very well handled specimen was all that was available. The quality of the images is dependent on the system used. I have tested the disk on several systems and some gave rise to problems in obtaining the correct colours. However, even on a notebook (with TFT screen) the picture was quite acceptable, though to obtain very detailed pictures with nuclear detail (important for some lymphomas) even an advanced high resolution screen was insufficient.

Who would benefit from this CD-ROM? The histopathologist who likes to work with atlases and computers who encounters an unusual spleen. He or she will need a textbook as well, to get information on differential diagnosis, clinical aspects, references, and so on.

J H J M VAN KRIEKEN

Book reviews

Inclusion-Body Myositis and Myopathies. Edited by V Askanas, G Serratrice, and W K Engel. (£80.00.) Cambridge University Press, 1998. ISBN: 0521 57105 7.

The sporadic form of inclusion body myositis is stated to be the commonest muscle disease to strike those over 50 years of age. A good multiauthored book on both hereditary inclusion body myopathies (h-IBM) and sporadic inclusion body myositis (s-IBM) would therefore be a welcome addition to the library of any department dealing with muscle biopsies. This book is a collection of reviews about IBM and is divided into six sections. The first section deals with comparisons (both pathogenic and pathological) between the hereditary IBM (h-IBM) and the sporadic forms (s-IBM) of IBM. There is extensive discussion of the diagnostic features on both light microscopy (including immunohistochemistry) and electron microscopy. Other sections deal with IBM viewed from a historical perspective, and there are also separate sections examining in detail the clinical and pathological aspects of both s-IBM and h-IBM (including atypical cases as well as other conditions characterised by basophilic rimmed vacuoles). The penultimate section deals with the mitochondrial abnormalities seen in IBM. Finally there is a section on possible treatment strategies. While reviewing the book I was examining a biopsy of a patient with possible IBM who also had evidence of HTLV-I infection. Not only did this book discuss a previous case and provide a reference; it also provided possible pathogenic mechanisms. Most chapters are well written and throughout the book the index appears to be helpful. In addition, there are up to date references. The majority of the 100 photographs are of very good quality.

My main criticisms are somewhat trivial. Figure 1.1 is placed in chapter 3, which is rather irritating. In addition, I feel that some of the introductions to chapters are a little repetitive and would have benefited from some editorial pruning. In summary, this is a well written book which I would certainly recommend to all those clinicians, pathologists, and researchers with an interest in muscle diseases. Although not primarily intended as a pathological bench book it does have some very useful contributions to make for any pathologist struggling with a possible case of IBM.

A KING

Introduction to the Blood–Brain Barrier: Methodology, Biology and Pathology. Edited by W M Pardridge. (£85.00.) Cambridge University Press, 1998. ISBN: 0 52158124 9.

The anonymous preface to this book claims that "adequate knowledge of the blood–brain barrier forms an essential component in the complete understanding of a large proportions of medical disciplines," and laments general ignorance on the structure, function, and investigative techniques appropriate for this important structure. The book itself attempts to redress this problem. To what extent does it succeed? The answer is almost completely, as both the contents and scope of the book belie a mere "introduction." The book comprises 50 chapters by a leading international group of basic and clinical scientists (including several distinguished pathologists!) and is divided into five sections concerning the methodology appropriate for the study of the blood–brain barrier, its transport biology, with more specific sections on signal transduction and biochemistry, and finally pathophysiology in disease states. The last of these sections proved to be the most instantly appealing, with a wide ranging series of excellent contributions, from microvascular abnormalities in dementia to multiple sclerosis and cerebrovascular disease with particularly interesting contributions on infectious diseases including HIV, cerebral malaria, and bacterial meningitis. The first section on methodology, containing a discussion of the clinical applications of barrier function methodology using MRI and PET technology, was particularly interesting and informative. The book has been well edited and produced, with numerous illustrations in monochrome. The index is excellent and the chapters are well